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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,414	09/30/2005	Keiichi Kawagoe	Q90666	4000

65565 7590 10/24/2008

SUGHRUE-265550
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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	PAPER NUMBER
1626	
MAIL DATE	DELIVERY MODE
10/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,414	KAWAGOE ET AL.	
	Examiner	Art Unit	
	REBECCA L. ANDERSON	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *7,8 and 16-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9-15* is/are rejected.

7)☒ Claim(s) *1-6 and 9-15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/12/2007; 9/30/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are currently pending in the instant application. Claims 1-6 and 9-15 are rejected and objected. Claims 7, 8 and 16-19 are withdrawn from consideration as being for non-elected subject matter.

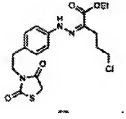
Election/Restrictions

Applicant's election without traverse of Group I and the further election of the compound (4-pyridinecarboxyaldehyde 4-(oxazole-5-yl)phenylhydrazone) in the reply filed on 8 July 2008 is acknowledged.

As per MPEP 803.02, the examiner will determine whether the entire scope of the claims is patentable. Applicants' elected species is not allowable. Therefore, according to MPEP 803.02:

> Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable **, the provisional election will be given effect and examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.
> the elected species shall be rejected, and claims to the nonelected species will be held withdrawn from further consideration.

As the elected species has been found not allowable, the Markush-type claims have been rejected and claims to the nonelected invention held withdrawn from further consideration. Additionally, the examiner has expanded the search and examination to the following compound:



Claims 1-6 and 9-15 have been examined to the extent that they are readable on the elected embodiment, the elected species and the additional species indicated above. Since the elected embodiment is not allowable, subject matter not embraced by the elected embodiment is therefore withdrawn from further consideration. Claims 7, 8 and 16-19 are therefore withdrawn from consideration as being for non-elected subject matter. It has been determined that the entire scope claimed is not patentable.

The requirement is still deemed proper and is therefore made FINAL.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The abstract of the disclosure is objected to because it is more than 150 words. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: Specifically, the specification does not include a cross-reference to related applications, see 37 CFR 1.78 and MPEP § 201.11.

Appropriate correction is required.

Claim Objections

Claims 1-6 and 9-15 are objected to as containing non-elected subject matter. Claims 1-6 and 9-15 presented drawn solely to the elected embodiment would overcome this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and

8. the level of the skill in the art.

Claims 1-6 and 9-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for products of the formula (I) or salt thereof, does not reasonably provide enablement for solvates of said product. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The nature of the invention

In the instant case, the claims are read as products of the formula (I) or salts, or solvates of said product.

The state of the prior art and the predictability or lack thereof in the art

In regards to solvates, according to Byrn, et al., "the occurrence of hydrated or solvated crystal forms, crystals in which solvent molecules occupy regular positions in the crystal structure, is widespread but *by no means universal among drug substances*." (emphasis added). Byrn, et al. "Solid State Chemistry of Drugs", 2d ed., SSCI, Inc., Ch. 10 Polymorphs, pp. 232-247, 232 (1999). Most drug crystals that fall into the category of solvates are hydrates. *Id.* at 236.

While the level of skill in pharmacology and organic chemistry is exceedingly high, there is no absolute predictability as to which solvates will function as intended. Byrn notes that the water molecule is particularly suited to fill structural voids, due to its small size. *Id.* In hydrated crystal structures, water molecules bind to other water molecules but also to any available functional group, i.e. carbonyls, amines, alcohols, and many others which are capable of accepting or donating an active hydrogen atom

to form hydrogen bonds. *Id.* Also, the behavior of hydrates of pharmaceuticals is unpredictable due to dehydration prior to melting, and cracking during dehydration. *Id.* at 234. Too, hydrates and solvates may only be formed under certain conditions, dependent upon the compounds sought to be crystallized. Such a process is not a given in pharmacology and requires a great deal of research, with no guarantee of success.

Furthermore, the stability of solvates and hydrates is not altogether predictable, wherein said stability directly affects the properties of a given molecule. This lack of stability means a hydrate or solvate, if found to possess similar properties as the target compound, may not function as intended *in vivo.* Such facts lead to the conclusion that more that a mere recitation is needed in order to support a claim to solvates and hydrates. Creating functional solvates and hydrates with the same properties as the mother-compound is by no means routine, thus there must be a showing sufficient to satisfy the enablement requirement.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present is for products of the formula (I) and salts (page 22). There is no direction or guidance as to preparing any solvate of the products of formula as claimed. There is no direction or guidance as to how and what molecules can be enclosed within the crystal structure of the instant compound.

The breadth of the claims

The breadth of the claims includes products of the formula (I), salts and solvates, thereof.

The quantity of experimentation needed and the level of the skill in the art

The level of difficulty required to produce functional hydrates and solvates is extremely high. The level of skill in pharmacology/organic chemistry is also very high. However, despite such a high level of skill in the requisite art, the creation of solvates and hydrates is unpredictable to the extent that undue experimentation is required in order to make and use solvates and hydrates of the claimed compounds. There is an insufficient showing in the Specification, or the state of the art does not acknowledge that the solvates and hydrates of the claimed compounds can be created via routine experimentation.

Therefore, Applicant's Specification does not enable one of ordinary skill in the art to make and use the invention commensurate in scope with the claims.

Claims 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for products of the formula (I) as agents for inhibiting aggregation of amyloid protein and agents for treating Creutzfeldt-Jakob disease (CJD) and Gerstmann-Straussler-Scheinker syndrome (GSS) does not reasonably provide enablement for agents for inhibiting aggregation and/or deposition of amyloid-like protein, for agents for the treatment of any other disease or agents for the prevention of any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention of claims 11-14 is agents for inhibiting aggregation and/or deposition of an amyloid protein or an amylid-like protein and treating or preventing a conformation disease such as Alzheimer's and Parkinson's disease. Furthermore, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological

activities (i.e. what compounds can treat or prevent which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Applicants are claiming methods which include the treatment and prevention of various diseases such as, Alzheimer's disease, Parkinson's disease, etc.

Applicants' claims are therefore drawn to the treatment or prevention of Alzheimer's disease. It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease.

(URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html.

Furthermore, Layzer, Cecil Textbook of Medicine, states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter theh progress of the disease" (pg. 1994).

It is the state of the art that in spite of the extensive studies performed on postmortem substantia nigra from Parkinson's disease patients, the aetiology of the disease has not yet been established (Mandel, 730) and despite the success obtained with animal models, clinical neuroprotection is much more difficult to accomplish. Additionally, animal models of Parkinson's disease may not be totally reflective of the disease and a single drug may not be adequate to induce neuroprotection (Mandel 730). Additionally, major consideration should be given to the optimal time at which to initiate the neuroprotective attempts and it must be aimed at the preclinical stage of the disease of which our ability to identify is currently very limited (page 752). The general failure to induce neuroprotection in the clinic versus in the laboratory with currently available drugs suggests that a single drug would not be sufficiently active and/or that the animal models we are employing are not truly representative of the disease state (page 752).

Additionally, Kawasaki et al. Journal of Virology, Dec. 2007, p. 12889-12898 only provides support for the elected compound for the treatment of CJD and GSS, not other

diseases. Also, the Kawasaki et al. article does not support the prevention of these diseases as the administration of the compound is only effective in prolonging the incubation periods, see page 12889.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment or prevention by the administration of the compounds of the claims one of skill in the art is unable to fully predict possible results from the administration of the compound.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of diseases applicant considers as treatable or preventable on page 1. Additionally, in vitro data is found on pages 191-193. Additionally, the disclosure does not provide how the in vitro data correlates to the treatment or prevention of the assorted diseases claimed.

The uses covered by the claims are not enabled based solely on the assay testing reported in the specification. Various studies reported for compounds in clinical development rely on animal models and not simply assay testing as done herein. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of in vivo use. Also see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a

reasonable expectation of in vivo success for any additional diseases that may still be embraced in response to this action. See MPEP 2164.05(a).

Further, there is no disclosure regarding how all types of diseases claimed having divers mechanisms are treated or prevented.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is agents for inhibiting aggregation and/or deposition of an amyloid protein or an amylid-like protein and treating or preventing a conformation disease such as Alzheimer's and Parkinson's disease. Furthermore, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of the multitude claimed would be benefited (treated or prevented) by the administration of the compound of the claims.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment or prevention of the various claimed diseases and disorders as a result necessitating one of skill to perform an exhaustive search for which disorders can be treated or prevented by what compounds of the instant claims in order to practice the claimed invention.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

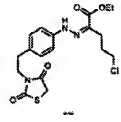
Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated or prevented by the compound encompassed in the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 and 9-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Moloney et al. (XP-002423191). Moloney et al. discloses the compound (58) in scheme 7a, page 2351:



which corresponds to applicants formula (I) wherein one of R1 or R2 is alkoxycarbonyl and the other is halogenoalkyl; R3 is hydrogen; Ar is phenylene; X is a linear alkylene having from 1 to 3 carbon atoms; and G is a saturated or unsaturated 5 to 7 membered heterocyclic group which is substituted with two oxo groups. It is noted that the medicament and agent claims 9 and 11-14 are only required to have the compound of formula (I). Additionally, while claim 10 required an pharmaceutically acceptable carrier, it is noted that page 2351 states that the hydrazone is heated in butanol (which is a topical pharmaceutical carrier).

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday from 6:00am until 2:30pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Anderson/
Primary Examiner, AU 1626

22 October 2008

Rebecca Anderson
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Art Unit 1626, Group 1620
Technology Center 1600